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EDITORIAL

Plasma renin levels: the lower the better in terms of cardiovascular risk?

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This editorial refers to 'Plasma renin and outcome in the community: data from PREVEND'†, by R.A. de Boehr *et al.*, on page 2351 of Volume 33 Number 18 September 2012

In 1898, Tigerstedt and Bergman discovered that a cortical extract of rabbit kidney has vasopressive properties when injected intravenously.[1] This is how a long and beautiful story started, leading to characterization of the renin–angiotensin–aldosterone system and to elucidation of its physiological and pathophysiological functions.[2–5] Presently, blockers of this system play a prominent role in the treatment of arterial hypertension, heart failure, diabetes, and nephropathy.[6,7]

Considerable progress was made when it became possible to assay renin in blood.[2–5] The regulation of renin secretion is complex, with a key role played by sodium balance. In man, the blood concentration of renin is inversely related to oral sodium intake. This relationship was taken into account in two studies seeking to evaluate cardiovascular risk in hypertensive patients, using stratification according to plasma renin activity level (low, normal, and high). The first study, by H.R Brunner and colleagues, showed an association of abnormally high renin secretion and increased risk of stroke or myocardial infarction.[8] Subsequently, these results were challenged, and two decades elapsed before their corroboration by Alderman and colleagues.[9] These authors reported that subjects with high plasma renin were at increased risk of cardiovascular events, notably myocardial infarction, results that were more convincing than the initial observations, due to a patient population (1717 hypertensive patients, as compared with 219 in the initial study). Nevertheless, this new result did not end the controversy surrounding the potentially deleterious impact of renin on cardiovascular risk.[10] Therefore, we must ponder on the best option for antihypertensive therapy. Is there any advantage in blocking the renin–angiotensin system of all patients, or should we target only those in whom renin is most likely to be elevated, based on criteria such as age? Should we be wary of stimulating the renin–angiotensin system if we prescribe a diuretic alone without a blocker of this system?[11]

The recent study by de Boer and colleagues provides the best evidence to date that plasma renin concentration has a prognostic value for the occurrence of cardiovascular events, independent of blood pressure level.[12] Several features of this work are worth mentioning. (i) The investigated cohort comprises a large number of adults ($n = 6228$), all living in the same city and having responded favourably to a written invitation for participation sent to all inhabitants of this city. The results are therefore likely to be representative for a general urban western population. (ii) Subjects were followed for an extensive period, on average $\sim$ 10 years. (iii) Enrolment was not restricted to hypertensive subjects, but was also open to normotensive subjects who had not incurred any cardiovascular complication such as stroke at the time of inclusion. (iv) When the cohort was subdivided according to quintiles of renin levels, the subgroups did not differ with respect to blood pressure and 24 h sodium excretion, making it possible to study the association of renin level with cardiovascular outcome independently of blood pressure and dietary sodium intake.

What do the results tell us? That high circulating renin levels are associated with increased cardiovascular morbidity and mortality, even after correcting for traditional risk factors.

From a clinical viewpoint, this observation is all the more relevant since it concerns a population of both hyper- and normotensive subjects. In this study, plasma renin levels were measured; these are known to correlate with plasma renin activity. Increased renin secretion is expected to augment the circulating concentrations of angiotensin II and perhaps also the production of angiotensin II at the tissue level.[13] It is to be regretted that the authors have not taken advantage of their enormous data bank also to assay active renin and prorenin, the latter being potentially involved in the tissue production of angiotensin II.[14,15] Wherever it is formed, this peptide plays a crucial role in the pathogenesis of vascular disease, in particular by inducing oxidative stress, which in turn triggers an inflammatory response.[16]

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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The treated hypertensive participants ($n = 843$) have not been taken into account in the primary analysis, but have been used for a subanalysis. In these patients, renin levels had no link to cardiovascular risk. Perhaps there were too few of them. The most likely explanation relates to the diverse effects of various antihypertensive agents on renin secretion. Whereas diuretics stimulate the renin– angiotensin system, beta-blockers—if devoid of intrinsic sympathomimetic activity—act in the opposite direction. Dihydropyridine-type calcium antagonists tend to increase renin secretion, but most often only transiently at the onset of treatment. Regarding angiotensin-converting enzyme inhibitors and antagonists of angiotensin II, they induce hyper-reninaemia, due to the inactivation of the negative feedback control normally exerted on renin secretion by angiotensin II. Here, a few thoughts are in order. Can monotherapy with diuretics be truly beneficial, considering that such therapy stimulates the renin–angiotensin system? If optimal prevention of cardiovascular complications is our goal, should we not systematically associate an antagonist of the renin–angiotensin system with a diuretic? Unfortunately, no answer to these questions is yet available. At the very most, we know that concomitant blockade of the renin–angiotensin system attenuates the metabolic effects of diuretics, which should be favourable in the long term.

The main message of the study by de Boer *et al.* is to confirm the association of high renin levels and increased cardiovascular risk. Based on this fact, some might propose the systematic assay of plasma renin as an additional tool for refining the stratification of cardiovascular risk. More practically, prescribing a blocker of the renin–angiotensin system could be considered in every patient with either hypertension, heart failure, or kidney disease, without determining the renin status. Such an approach would be expected to be of benefit not only to patients with high renin levels, but also to those with normal or low renin levels.

Conflict of interest: none declared.

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